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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WALICKA, MALGORZATA A	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 03/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/724,571	ANDERSON ET AL.	
	Examiner	Art Unit	
	Malgorzata A. Walicka	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *Nov. 3, 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *78-85,132 and 135* is/are pending in the application.

4a) Of the above claim(s) *79,80 and 132* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *78, 81- 85 and 135* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

The Amendment to claims, filed on Nov. 3, 2003 and amendments to drawings and specification filed on Nov. 10, 2003 are acknowledged. The Amendments were filed in response to the Office Action of May 1, 2003, which was the first Office Action. Due to inadvertent and misleading markings of both "Non-final" and "Final" boxes in the Office Action Summary, the Applicant treated the first Office Action a final.

The instant Office Action is the second Office Action. Claims 1-77 and 86-131 are cancelled; claims 79, 80 and 132 are withdrawn as directed to the non-elected invention. Claims 78, 81-82, 84 are amended; new claim 135 is added. Claims 78, 81-85 and 135 are currently under examination and are the subject of this Office Action.

DETAILED ACTION

1. Objections

1.1. Specification

The objection to claims 78 and 84 made in the previous Office Action is withdrawn, because the claims have been amended.

The amended description of Fig. 5 is unclear. The examiner proposes the following:

FIG. 5 shows the full-length amino acid sequence of beta–secretase, i.e. amino acid residues 1-501 (SEQ ID NO: 2), and the ORF, which encodes it (SEQ ID NO: 1). Certain features are indicated, such as "active-D" sites indicating the aspartic active

catalytic sites, a transmembrane region commencing at position 453, as well as leader ("signal") sequence (residues 1-21; SEQ ID NO: 46) and the putative pro region (residues 22-45; SEQ ID NO: 47). The polynucleotide encoding mature form of the protein of SEQ ID NO: 2, i.e., amino acids 46-501 (SEQ ID NO: 43) corresponds to nucleotides 135-1503 of SEQ ID NO: 1 and is identified as SEQ ID NO: 44.

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors in the specification of which applicant may become aware.

1.2. Claims

Claim 82 recites the phrase "ß-amyloid precursor protein" which is unnecessary; the abbreviation ß-APP has been already expanded in claim 78.

Claim 78, 83, and 84 are objected to for lack of consistency in writing the abbreviation ß-APP.

Claim 135 is objected to for using the word "comprised" instead of "comprising".

2. Rejections

2.1. 35 USC, section 101

Rejection of claims 81 and 82 under 35 U.S.C. 101 made in the previous Office Action is withdrawn, because the claims have been amended.

2.2. 35 USC, section 112, second paragraph

Rejection of claims 78, and 81-83 in the previous Office Action is withdrawn, because the claims have been amended.

Claims 78 and 84 are rejected because they are confusing. The quoted sequences SEQ ID NO: 103 and 104 do not identify human beta amyloid precursor protein wild type and its Swedish mutation but their fragments that are beta-secretase substrates. Both fragments are four amino acid long and cannot be shorten.

2.3. 35 USC, section 112, first paragraph

2.3.1. Lack of written description

Rejection of claim 82 under this paragraph for the reasons stated in the previous Office Action is withdrawn, because the claim has been amended.

2.3.2. Scope of enablement

Claims 78, 81-85 and new claim 135 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *in vitro* testing, does not reasonably provide enablement for *in vivo* testing. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The claims are directed to the method of *in vitro* and *in vivo* testing a chemical compound for its ability to inhibit beta-secretase, wherein the *in vitro* part of the method uses as substrates of said beta-secretese polypeptides of SEQ ID NO:104 and 83.

In vivo testing, performed on transgenic animal that encompasses a DNA molecule that encodes a human beta-amyloid precursor protein, uses as a proof of inhibiting of Aβ production an improvement of cognitive ability or reduced plaque burden.

The specification fails to disclose the steps of the method of the claims 81, particularly how to obtain a transgenic animal from any animal, the way the tested compound is to be administered to a mammal and how to measure the cognitive abilities and plaque burden. Claim 82 lacks the teaching how to identify a mammal that is characterized by deposits of Aß and how to obtain from it a transgenic mammal that is characterized by deposits of Aß, and comprises DNA encoding human beta-amyloid precursor protein. Therefore, to make and use the claimed invention undue experimentation is necessary.

Factors to be considered in determining whether undue experimentation is required are summarized *In re* Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim.

The nature and breadth of the claimed invention encompasses a test using any mammal characterized by Aβ peptide deposits. This includes the animal that additionally has to be transfected with a gene encoding a human β-amyloid precursor

protein or its variant and/or a transgene encoding beta -secretase. The claims are also directed to the extremely large number of chemical molecules, as any chemical compounds is to be administered. Assessment of the treatment efficacy comprises measuring "cognitive ability", which is a generic term including several species, none of them is taught by applicants.

Although the studies of Alzheimer disease are well developed and the skill of artisans high, no one is able;

a) to test all animals for the level of Aβ peptide deposit, and select any one having the high level of said deposit and produce from said animal(s) transgenic species comprising a human β-amyloid precursor protein, and any beta-secretase,

b) to develop the way of administration to said animal of any chemical compound that can be considered as a candidate inhibitor of β-secretase; said way includes finding the proper solvent, dose, frequency and time of administration to avoid lethal effects and diminish side effects,

c) to measure the level of Aβ peptide deposits and/or cognitive ability of the treated animal before and after the appropriate time of treatment.

The disclosure is silent about any of the steps a)-c). Also, the disclosure is not enabling for any beta-secretase, but the human beta secretase whose sequences are disclosed.

Without further guidance on the part of applicants regarding the experimental animal, beta-secretase encoding sequences and chemical compound to be used, as

well as without teaching the details of the compound administration and measurements of the level of Aβ peptide deposits and measurements of cognitive abilities, experimentation being left to the skilled artisan has a low probability of success.

In summary, one skilled in the art who wants to make and use the instant invention is forced to perform experimentation that is improperly extensive and undue.

Traversing this rejection in the part regarding animal subject and transgenic animal subject, Applicants indicate that the he specification discusses rodent lines that express the human beta-APP gene (page 7 line 14 of the Remarks). Although this is true, claims 81 and 82 are not limited to rodents, therefore the argument is found not persuasive.

Traversing this rejection in part concerning enablement of the way of administration of any chemical compound that can be considered as a candidate inhibitor of β-secretase Applicants write, on page 8, line 13 of their Remarks: "Applicants point to page 54, line 16 to page 55 line 3 of the specification which discusses the administration of test compounds, including the routes of administration, dose ranges, and methods well know in the art to determine routes of administration and dosage ranges."

Applicants' argument has been fully considered, but is found not persuasive. The quoted passage reads as follows:

"Compounds or agents found to be efficacious and safe in such animal models will be further tested in standard toxicological assays. Compounds showing appropriate toxicological and pharmacokinetic profiles will be moved into human clinical trials for treatment of Alzheimer's disease and related disease. The same screening approach can be used on other potential agents such as peptidomimetics described above.

In general, in selecting therapeutic compounds based on the foregoing assays, it is useful to determine whether the test compound has an acceptable toxicity profile, *e.g.*, in a variety of in vitro cells and animal model(s). It may be useful to search the tested and identified compound(s) against existing compound databases to determine whether the compound or analogs thereof have been previously employed for pharmaceutical purposes, and if so, optimal routes of administration and dose ranges. Alternatively, routes of administration and dose ranges can be determined empirically, using methods well known in the art (see, *e.g.*, Benet, L. Z. *et al.* Pharmacokinetics in *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, Ninth Edition, Hardman, J. G., *et al.* Eds., McGraw-Hill, New York, 1966) applied to standard animal models, such as a

transgenic PDAPP animal model (e.g., Games, D., *et al.*, Nature 373: 523-527, 1995; Johnson-Wood, K., *et al.*, Proc. Natl. Acad. Sci. USA 94: 1550-1555, 1997). To optimize compound activity and/or specificity, it may be desirable to construct a library of near-neighbor analogs to search for analogs with greater specificity and/or activity. Methods for synthesizing near-neighbor and/or targeted compound libraries are well-known in the combinatorial library field.

C. Inhibitors and Therapeutics"

One skilled in the art notes that the passage suggests, in general terms testing, whether the test compound has an acceptable toxicity profile using a variety of *in vitro* cells and animal model(s). However, Applicants do not define the meaning of the term "acceptable toxicity profile". One skilled in the art also understands that Applicants suggest, in general terms, determination of routes and dose range empirically, based on publications that are not incorporated in the specification by reference. However, Applicants themselves do not teach any way of administration, to an animal having high level of Aβ peptide deposit and/or being a transgenic animal, of any chemical compound that can be considered as a candidate inhibitor of β-secretase. The disclosure is silent as to finding the proper solvent, dose, frequency and time of administration to avoid lethal effects and diminish side effects.

Traversing the rejection in part concerning enablement for measuring the level of Aβ peptide deposits and/or cognitive ability of the treated animal, Applicants state, "Measurement of cognitive ability of mammalian subjects was well known in the art at the time of filling the instant application, *e.g.,* see pages 39-42 and Example 9 of WO/9640896. Measurement of plaque burden was also well known in the art at the time of filling the instant application, *e.g.,* see pages 51-52 and Example 6 of WO/9640896" (page 8 line 16 of Remarks).

Applicants' argument has been fully considered, but is found not persuasive. The quoted WO document is not incorporated by reference nor listed in the Information Disclosure Statement. The specification is silent as to how to measure cognitive ability and Aβ peptide deposits.

In summary, one skilled in the art concludes the Applicants' suggestions do not consist a guidance and/or instruction that would prevent undue experimentation, thus the invention remains rejected for the scope of enablement.

2.4. *35 USC section 103*

The rejection of claims 78, 81-85 made in the previous Office Action under 35 U.S.C. 103(a) as being unpatentable over WO96/40885, WO 98/37226 and further in view of US Patent No. 6,319,689, issued to Powell et al. is withdrawn because the human beta-secretase sequence disclosed by Powell et al. does not comprise polypeptides being fragments of SEQ ID NO: 2 without amino acids residues 1-22 or 1-45 that are products used in the instant invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka, Ph.D., whose telephone number is (703) 305-7270. The examiner can normally be reached Monday-Friday from 10:00 a.m. to 4:30 p.m.

If attempts to reach examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, Ph.D. can be reached on (703) 308-3804. The fax phone number for this Group is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionists whose telephone number is (703) 308-0196.

Malgorzata A. Walicka, Ph.D.

Patent Examiner

Art Unit 1652